one case, as the authors point out, the patients have more "severe" primary hyperparathyroidism than we in the U.S. commonly observe.[4] In the second study, the hyperparathyroid patients have a densitometric profile similar to normal women, which the authors postulate is because the parts are significantly heavier than eucalcemic controls.[3] The patients we see are not heavier than normal and have uniform evidence for demineralization at cortical sites. Furthermore, the control group in the second study is somewhat unusual. Despite the menopausal status of the control subjects, they gained bone mass at the lumbar spine during the period of observation.

There is a subgroup of postmenopausal women with asymptomatic primary hyperparathyroidism who do lose bone mass[5]; these individuals become menopausal while they are hyperparathyroid. Their rate of bone loss at the lumbar spine is similar to that of normal early menopausal women. It is unclear how many of the women in the studies cited by Grey fell into this category. In this regard, estrogen treatment in primary hyperparathyroidism[4,6] needs further delineation in the subgroup of women just entering the menopause.

While it may be impossible to extrapolate the observations of Grey et al. and Guo et al. to a cohort of patients with asymptomatic primary hyperparathyroidism in the United States, we fully agree with Dr. Grey's ultimate conclusions. Until an effective medical therapy for primary hyperparathyroidism is available, patients who are managed without surgery require continued monitoring of bone density. We have not yet detected which indices, if any, might be predictive of the patients with primary hyperparathyroidism who do lose bone.

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Letter to the Editor

Further Study of the Therapy for Fibrous Dysplasia Is Necessary

To the Editor:

While Dr. Weinstein's clinical experience with bisphosphonate therapy of fibrous dysplasia has been favorable, the evidence presently available cannot justify the conclusion that this "previously medically untreatable bone disease is now amenable to aminobisphosphonate therapy."[1] Although we share his optimism, we feel the issues of medical therapy for this devastating disease deserve more space than may have been available in Dr. Weinstein's article.

To place this study in context, Dr. Weinstein's patient has responded better than many early patients given calcitonin, mithramycin, and the bisphosphonates clodronate and etidronate.[2–5] Despite modest biochemical evidence of effect, none of these case reports described pain control, stabilization/improvement of bone structure, or fracture prevention.

Only with the more potent bisphosphonates has evidence of effectiveness been seen. Liens et al. used pamidronate in 9 patients.[6] Consistent with Dr. Weinstein's experience, bone turnover decreased, and pain was lessened in 12/14 lesion sites. However, radiological improvements were only reported in 4/9 patients, and one child developed a rachitic mineralization defect of the growth plate. In a similar pamidronate trial, Bone et al. confirmed a variable improvement in pain and stabilization of lesion expansion with some evidence of lytic repair and occasional progression.[7]

Despite this trend of evidence, the fact that none of the above studies have been blinded or controlled begs attention. The natural history of fibrous dysplasia in any individual may be subclinical, waxing and waning, or progressive.[8] Thus a properly blinded, randomized, and controlled study will be required to prove effectiveness. Until these data are available, the uncertainty of benefit and the risks of such therapy, particularly in growing children, should be fully described to patients and their parents.

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Reply

Wait for Study or Treat? Treat

To the Editor:

I read with interest the letter of Czerwiec and colleagues concerning my report of a young lady with fibrous dysplasia and a remarkable response to aminobisphosphonate treatment.[1] I, of course, agree that a blinded, randomized, and controlled study would be the ideal vehicle for unequivocally establishing the effectiveness of aminobisphosphonates in this devastating disease. However, the ability to organize such a study given the relatively infrequent occurence of the condition, and the consequent interminable delays in obtaining results, raises significant ethical questions regarding the wisdom of withholding treatment while waiting for results of a controlled trial in a rare and highly variable disease. I also agree that patients and parents should be fully informed of the current status of knowledge regarding the benefits and the risks of such therapy; this certainly was the case with this young lady and her mother. Furthermore, the letter of Czerwiec et al. voices, in my opinion, an unsubstantiated alarm regarding the risks of aminobisphosphonates while it underplays the existing experience with the use of these drugs.

Contrary to the concerns of Czerwiec et al., sufficient evidence is available to support the safety and efficacy of aminobisphosphonate treatment for fibrous dysplasia,[1–4] and the National Foundation for Paget's Disease of Bone and Related Disorders has recommended aminobisphosphonates for the nonsurgical management of this condition.[5] Moreover, the vignette in the Journal[1] argues strongly that the dramatic improvement in pain, as well as the biochemical, densitometric and radiographic amelioration of the disease were the result of the therapy rather than the results of waxing and waning of its natural progression. Spontaneous improvement in a painful, expanding lytic lesion of the femoral neck has not been noted by workers experienced with fibrous dysplasia and, instead, fracture would be the far more likely outcome, a sequela avoided by the aminobisphosphonate treatment.

The concerns of Czerwiec and colleagues about rachitic changes were based on a report of a 13-year-old patient with fibrous dysplasia who was treated with three courses of intravenous pamidronate and showed an increase in growth-plate thickness at the knee.[3] It is worth noting, however, that Liens et al. also reported that these radiographic findings resolved spontaneously. In rapidly growing children, the radiographic appearance of the medial side of the knees may appear thickened but the cardinal signs of rickets (irregular and bulging metaphyses with concavity at the metaphyseal ends) remain absent. More importantly, hyperparathyroidism has a predilection for the medial sides of the femora and tibiae at the knees and may be easily mistaken for rickets.[6] The radiographic changes noted in the patient described by Liens et al. are more likely the result of pamidronate-induced secondary hyperparathyroidism. The inhibition of osteoclasts by bisphosphonates in a growing skeleton may cause a transient decrease in the serum ionized calcium level and an increase in parathyroid hormone secretion[7,8] although these events are virtually always clinically asymptomatic. It is, however, important to exclude vitamin D deficiency and provide adequate vitamin D and calcium supplementation before initiation of such therapy. Studies of young patients with severe osteoporosis treated with aminobisphosphonates clearly demonstrate the safety and efficacy of these compounds.[9]

Aminobisphosphonates should be offered to symptom-

atic children and adolescents with fibrous dysplasia by physicians knowledgeable about the disease and experienced with this type of therapy, as there are no effective alternatives and the benefits, documented in my report, far exceed the risks.

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